VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing VICH GL33

DRAFT GUIDANCE

(For Comment Purposes Only)

This draft guidance outlines a testing approach to assure human food safety following the consumption of food products derived from animals treated with veterinary drugs.

Comments and suggestions regarding the document should be submitted to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 02D-0326.

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Center for Veterinary Medicine
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STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: GENERAL APPROACH TO TESTING

Recommended for Consultation
at Step 4 of the VICH Process
on 11 April 2002
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND IS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT WILL BE RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

GENERAL APPROACH TO TESTING

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This draft guidance represents the agency's current thinking and does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative method may be used as long as it satisfies requirements of the applicable statutes and regulations.

1. INTRODUCTION

1.1. Objective of the guidance

This guidance outlines a testing approach to assure human food safety following the consumption of food products derived from animals treated with veterinary drugs. It represents harmonization of toxicology testing guidances in the international community. The selection of concise and appropriate tests was of major concern in the development of the guidance. A test regimen was selected based on a minimum number of tests after consideration of extensive historical data and review of widely accepted protocols. These tests should provide the adequate amount of useful toxicological data to ensure human food safety, while reducing the number of animals used in testing and conserving resources. Whenever possible, flexibility, minimum number of animals, as well as alternative *in vivo* and *in vitro* tests, are included in the approach.

1.2. Background

The human hazards associated with the consumption of food products containing drug residues are assessed in laboratory animals treated with veterinary drugs. International harmonization of testing requirements assures that the development and registration of valuable animal drugs is achieved with maximum efficiency. The efficiency of the approval process has an impact on the expenditure of resources, time from discovery to new product approval, and the introduction of innovative drugs into the market.

Existing toxicological testing recommendations for veterinary drugs have evolved from the toxicological tests for human medicines, food additives and pesticides. The following guidance was developed to include tests particularly relevant to the identification of a no-observable adverse effect level (NOAEL) for veterinary drugs.

The appropriateness of a test for the purpose of assessing human food safety is defined in terms of its ability to predict an adverse effect in humans. To increase the chance of identifying a potential human adverse effect, rodent and non-rodent models should be included in the *in vivo* testing approach. Other additional studies, such as testing for effects on the human intestinal microflora, may be used to evaluate compound specific end-points. A testing approach should be designed to determine a dose that causes an adverse effect and a dose that can be identified as the NOAEL. A NOAEL is used to establish a human acceptable daily intake (ADI) which represents the amount of drug that can be safely consumed by a person on a daily basis for a lifetime.

1.3. Scope of this guidance

The scope of this guidance is to identify: 1) basic tests recommended for all new animal drugs used in food-producing animals to assess the safety of drug residues present in human food, 2) additional tests recommended based on specific toxicological concerns associated with the structure, class, mode of action, etc. of the drug and 3) special tests which might be useful in the evaluation of the relevance or the interpretation of data obtained in the basic or additional tests.

Guidance on the design of protocols for tests recommended as basic and additional tests will be provided in separate VICH guidances. Selection and protocol design of special tests should be left to the discretion of the various regulatory authorities and/or drug sponsors.

2. GUIDANCES

Testing includes an assessment of systemic toxicity, reproduction toxicity, developmental toxicity, genotoxicity and carcinogenicity. In general, oral administration should be the route of choice for *in vivo* tests unless experimental technique suggests a different route of administration. The guidances do not preclude the possibility of alternative approaches that may offer an equivalent assurance of safety, including scientifically based reasons as to why such data may not need to be provided.

2.1. Basic tests

2.1.1. Repeat-dose toxicity testing

Repeat-dose toxicity testing in one rodent and one non-rodent animal species should be performed to define (1) toxic effects based on repeated and/or cumulative exposures to the compound and/or its metabolites, (2) the nature of the tissue/organ damage, particularly in relation to dose and/or duration of exposure, (3) dosages associated with toxic and biological responses, and (4) a NOAEL.

2.1.2. Reproduction toxicity testing

Multigeneration reproduction studies should be designed to detect any effect of the parent substance or its metabolites on mammalian reproduction. These include effects on male and female fertility, mating, conception, implantation, ability to maintain pregnancy to term, parturition, lactation, survival, growth and development of the offspring from birth through to weaning, sexual maturity and the subsequent reproductive function of the offspring as adults.

2.1.3. Developmental toxicity testing

The aim of developmental toxicity testing is to detect any adverse effects on the pregnant female and development of the embryo and fetus consequent to exposure of the female from implantation through the entire period of gestation to the day before caesarean section. Such adverse effects include enhanced toxicity relative to that observed in non-pregnant females, embryo-fetal death, altered fetal growth, and structural changes.

2.1.4. Genotoxicity testing

A battery of genotoxicity tests should be used to identify substances that have the capacity to damage the genetic information within cells. Substances that are considered to be genotoxic are regarded as potential carcinogens. Those that cause genetic damage in germ cells also have the potential to cause reproductive/developmental effects.

2.2. Additional tests

These tests are recommended to address safety concerns based on compound structure, class, mode of action, etc. Some examples of these studies are:

2.2.1. Testing for effects on the human intestinal microflora

For compounds with antimicrobial properties, information to determine the safety of residues on the human intestinal microflora is recommended.

2.2.2. Pharmacological effects testing

Some veterinary drugs produce pharmacological effects in the absence of a toxic response or at doses lower than those that elicit toxicity. The pharmacological NOAEL should be identified and taken into account in the setting of the ADI for the drug.

2.2.3. Immunotoxicity testing

For some classes of drugs such as beta-lactam antibiotics, the potential for the drug to elicit an allergic reaction in sensitive individuals should be investigated. Immunotoxicity testing may be recommended for other veterinary drugs when the results from other tests indicate a potential immunological hazard.

2.2.4. Neurotoxicity testing

If evidence of a neurotoxic potential is identified in repeat-dose tests further testing, such as testing in accordance with OECD Test Guideline 424 “Neurotoxicity Study in Rodents,” may be recommended.

2.2.5. Carcinogenicity testing

For compounds that are considered potential carcinogens, oral carcinogenicity tests are recommended. The decision to recommend carcinogenicity testing is based on all available data including results of genotoxicity testing, structure activity relationship (SAR) information and results of repeat-dose and mechanistic studies. It is recommended that carcinogenicity testing be performed using a carcinogenicity bioassay (OECD Test Guideline 451 “Carcinogenicity Studies”). However, information derived from a combined assay for carcinogenicity and chronic toxicity (OECD Test Guideline 453 “Combined Chronic Toxicity/Carcinogenicity Studies”) would also be acceptable.

2.3. Special tests

These are tests performed to understand the mode of action of the drug and used to aid in the interpretation of, or the assessment of, the relevance of the data obtained in the basic and/or additional tests.